EXHIBIT 606.C

Digoxin Dosing Calculator

Determination of initial loading and maintanance dose.

All calculations must be confirmed before use. The authors make no claims of the accuracy of the information contained herein; and these suggested doses are not a substitute for clinical judgement. Neither GlobalRPh Inc. nor any other party involved in the preparation of this program shall be liable for any special, consequential, or exemplary damages resulting in whole or part from any user's use of or reliance upon this material.

If steady state levels are available, use this table instead.
Click here or program information.

Patient name: **Floor:**

Age: 70 | Male | **Scr**(mg/dl): 1

Height: 70 Centimeters | **Weight:** 70 Kilograms

Select disease state: CHF

Enter desired Cpeak: 1.0 **Dosage form:** Tablets **Acute CHF?** No

Interacting drugs: No interacting drugs

Dosing schedule: Daily dosing

Calculate Reset

References:

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EXHIBIT
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PENGAD 800-631-6989

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Disclaimer

Digoxin Dosing - D. McAuley, GlobalRPh Inc.

There are many problems encountered in writing a program to effectively dose a drug such as digoxin. It is inherently difficult because of such components as narrow therapeutic index, difficult to define therapeutic endpoints, inter and intra-patient variability, and varying effects of pathological states and drugs on digoxin's disposition. In sum, there exists significant variability as far as a given dose and concentration produced in a given patient. It is important to be able to determine various patient attributes that may help predict drug concentrations for any given patient. There are several known attributes that have a direct correlation with the eventual therapeutic dose. Variables such as ideal body weight, serum creatinine, age, concomitant drug therapy all have great influence on the eventual therapeutic dosing regimen. The mathematical "backbone" of this program is based on the references below. You will notice two sets of responses when using this program. The first result is based on the "Jelliffe" method which attempts to predict the percentage of digoxin eliminated in a 24 hour period and the dose of digoxin required to maintain the concentration in the therapeutic range. The other result is based primarily on the "Jusko equations (below) and "Koda-Kimble" which attempts to calculate the effective digoxin clearance. After estimating the digoxin clearance, it is possible to make predictions regarding the steady state concentration:

Css = (Maint dose x F) /(dig cl x T)

F= bioavailability factor
T= dosing interval
dig cl= digoxin clearance obtained as noted above.

The "Jusko" Dosing section is based on the following equations.

Initial dosing

1. Estimate Volume of Distribution (Jusko Equation)

Vd = 226 + [(298 x CrCl) / (29.1 + CrCl)] x (BSA / 1.73)
where CrCl = normalized creatinine clearance(ml/min)
BSA = Body surface area (square meters)

C-3

2. Calculate Loading Dose

LD = Vd x Cp/F

where Vd = Volume of distribution (liters)

Cp = target serum level (mcg/l)
F = bioavailability factor:

· IV push = 1
· capsules= 0.95
· elixir = 0.8
· tablets = 0.75

3. Estimate Clearance (Koda-Kimble)

Cl = [(A x CrCl) + B] x C

where A = 0.88, for patient with Acute CHF, otherwise=1

B = 23, for patient with Acute CHF, otherwise=40
C = correction factor for interacting drugs:

· Quinidine = 0.65
· Spironolactone = 0.75
· Verapamil = 0.7
Other= 0.71

4. Calculate Maintenance Dose

MD = (Cl x Cp x tau) / F

where Cl = Clearance (liters/hour)

Cp = target serum level (mcg/l)
tau = dosing interval (hours)
F = bioavailability factor

5. Estimate steady-state trough level

Cpss = (MD x F) / (Cl x tau)

where MD = Maintenance dose (mcg)

F = bioavailability factor
Cl = Clearance (liters/hour)
tau = dosing interval (hours)

Adjust maintenance dose

1. Estimate Volume of Distribution (Jusko Equation - see above)

2. Calculate digoxin clearance

Cl = [(MD x F) / Cp] / tau

where MD = Maintenance dose (mcg)

F = Bioavailability factor
Cp = Steady-state serum digoxin concentration (mcg/l)
tau = Dosing interval (hours)

3. Calculate Maintenance Dose

MD = (Cl x Cp x tau) / F

where Cl = Digoxin clearance (l/hr)

Cp = target serum level (mcg/l)
tau = dosing interval (hours)
F = bioavailability factor

4. Estimate steady-state trough level

Cpss = (MD x F) / (Kel x Vd x tau)

where MD = Maintenance dose (mcg)

F = bioavailability factor
Kel = Elimination rate (1/hours)
Vd = Volume of distribution (liters)
tau = dosing interval (hours)

These equations were provided by Rick Tharp of RXkinetics (http://www.rxkinetics.com). His site contains additional information on digoxin dosing as well as several other clinical areas.

General info:

Loading dose: CHF: 8-12 mcg/kg in divided doses (q4-8h) over 12 to 24 hours.

[Normally, give 50% of the total digitalizing dose in the initial dose, then give 25% of the total dose in each of the two subsequent doses at 8 to 12 hr intervals- Obtain EKG 6 hours after each dose to assess potential toxicity (AV block, sinus bradycardia, atrial or nodal ectopic beats, ventricular arrhythmias); Other: vision changes, confusion.] If pt has **renal insufficiency** give 6 to 10 mcg/kg IBW. **A-fib:** 10 to 15 mcg/kg IBW given as above. (If given IVPush-admin over at least 5 min). **Maintenance dose:** Digoxin clearance= [CRCL + 40] x 1.44 (add 20 instead of 40 if pt has CHF). Predicted Css= (Dose) (0.65 to 0.8)/ Digoxin clearance. Alternatively, maint dose= Loading dose x [0.14 + crcl/500] Avoid IM injections-can lead to severe pain (If it must be given by this route, give deep IM followed by massage). **Monitoring**: Obtain blood samples at least 4 hrs after IV dose and 6-8hrs after oral dose. **Serum levels**: 0.5 to 2.0 ng/ml. Obtain first level within 24 hours of digitalization. Monitor BUN and serum creatinine q2days (qd if unstable). Monitor apical pulse daily.. **Onset/peak: IV**: 5-30min/ 1-4hrs **Oral**: 1-2hrs/ 2-8 hrs. Time to steady state: 5-7 days (average) ESRD: 15-20 days. Half-life: 38-48 hrs. (anephric: 4-6 days). **Conversion from oral to IV**: Decrease IV dose by 20 to 25%. When the maintenance dose is given IV, the onset and peak will occur earlier, however the duration of action is the same. Patients' on the "floors" may receive once daily IV maintenance doses, however, IV loading regimens (multiple doses) are restricted to pts on a monitor- ICU's. [Oral bioavailability (tablets): 70 to 80%].

Factors that increase likelihood of digoxin toxicity: Hypokalemia, hypomagnesaemia, hypothyroidism, renal dysfunction, interacting drugs (eg quinidine, verapamil).

Distribution: only a small fraction of digoxin in present in blood (little is removed by hemodialysis). Digoxin distributes very little into body fat--doses must be based on lean body weight. Distribution is not altered by obesity. There appears to be a gradual contraction in the volume of distribution as renal function deteriorates. Therefore, extreme caution is necessary when dosing patients with renal failure.

Maximal response from any maintenance dose of digoxin will be obtained when serum concentrations are at steady state and maximal body stores for that dose have been obtained. It should be noted that any adjustment of dose or change in the elimination of digoxin requires a waiting period of 4-5 times the half-life (1 week with normal renal function) before the new steady state concentration is achieved.

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